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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): 66802.055

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on Filed electronically on 11/18/2011

Signature

Typed or printed name KATHRYN L. HESTER, Ph.D.

Application Number	Filed
10/669,925	09/24/2003
First Named Inventor	
William H. Hildebrand	
Art Unit	**Examiner**
1644	M. DiBrino

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- [ ] applicant/inventor.
- [ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- [x] attorney or agent of record. Registration number 46,768
- [ ] attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

Signature

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11/18/2011
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

- [x] *Total of 1 forms are submitted.

ELECTRONICALLY FILED: **NOVEMBER 18, 2011** **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Hildebrand et al.	)	Atty Dkt No:	66802.055
		)		
Serial No:	10/669,925	)	Examiner:	M. DiBrino
		)		
Filed:	September 24, 2003	)	Art Unit:	1644
		)		
Customer No.:	30589	)	Confirmation No.:	4622

For: ANTI-HLA ASSAY AND METHODS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Applicants respectfully request review of the Final Office Action mailed May 23, 2011 in the above-identified application. No amendments are being filed with this request, and this request is being filed with a Notice of Appeal.

In the Final Office Action, the Examiner rejected claims 31-37, 45, 46, 49-51, 60 and 61 under 35 U.S.C. 103(a) as being unpatentable over US 5,482,841 in view of McCluskey (J. Immunol. 1988, 141:1451-1455), Prilliman (Immunogenetics, 1997, 45:379-385), DiBrino (Biochemistry, 1995, 34(32):10130-10138), Hausmann (Clin. Exp. Immunol. 1993, 91:183-188) and Chen (J. Immunol. 1994, 152:2874-2881). Also in the Final Office Action, the Examiner rejected claim 48 under 35 U.S.C. 103(a) as being unpatentable over the combination of references above and further in view of Nakahima (Nucleic Acids Res. 1997, 25:2231-2232). Applicants respectfully traverse the rejections and submit that a *prima facie* case of obviousness has not been established for either rejection. Arguments in support of Applicants' position can be found on Pages 8-16 of the Amendment and Response filed March 14, 2011 (incorporated herein by reference), as well as the following comments.

The presently disclosed and claimed inventive concept(s) is directed to a method for detecting the presence of anti-class I MHC complexes. In the method, a pool of functionally active, recombinantly produced, truncated individual soluble class I MHC trimolecular complexes that have been purified substantially away from other proteins is obtained. ***Each complex present in the pool contains the same truncated, individual class I MHC heavy chain molecule.*** At least one soluble class I MHC trimolecular complex from the pool is then linked to a substrate (directly or indirectly) such that the trimolecular complex retains the physical, functional and antigenic integrity of a native complex. A sample is then reacted with the substrate/complex, and the substrate is washed to remove unbound portions of the sample. The substrate/complex is then reacted with means for detecting anti-class I MHC antibodies, and it is determined that anti-class I MHC antibodies specific for the individual class I MHC molecule are present in the sample if the means for detecting the anti-class I MHC antibodies is positive.

The pool of functionally active, recombinantly produced, truncated individual soluble class I MHC trimolecular complexes is obtained by isolating mRNA encoding a class I MHC heavy chain allele from a source, reverse transcribing the mRNA to obtain cDNA, and identifying an individual class I MHC heavy chain allele in the cDNA. The identified allele is then subjected to PCR amplification. The PCR amplification results in a PCR product that encodes a truncated, soluble form of the desired individual class I MHC heavy chain, whereby the PCR product does not encode the cytoplasmic and transmembrane (TM) domains of said molecule. The PCR product is then inserted into a mammalian expression vector that is inserted into a mammalian cell line, which is then cultured under conditions that allow for (1) expression of the recombinant individual soluble class I MHC heavy chain molecule; (2) endogenous loading of a peptide ligand; and (3) non-covalent association of beta-2-microglobulin to form the individual soluble class I MHC trimolecular complexes that are secreted from the cell. The soluble class I MHC trimolecular complexes so produced are naturally assembled within the cell to form heterotrimers comprising: (1) the recombinantly introduced desired **soluble** class I MHC heavy chain; (2) **non-covalently associated** light chain (β2m) that is native to and endogenously produced by the host cell; and (3) **naturally produced and endogenously loaded** antigenic peptides. The soluble class I MHC trimolecular complexes are harvested from the culture while the the mammalian cell is retained in culture to allow for continuous production of additional soluble class I MHC complexes. The soluble class I MHC trimolecular complexes are then purified substantially away from other proteins and maintain the physical, functional and antigenic integrity of the native class I MHC trimolecular complex.

As is well known (but often hard to effectuate in practice), there are three factual inquiries required for determining the obviousness of a claim: (1) the scope and content of the prior art are to be determined; (2) differences between the prior art and the claims at issue must be ascertained; and (3) the level of ordinary skill in the pertinent art resolved. *Graham v. John Deere Co.*, 383 U.S. 1 (1966). The Federal Circuit and Supreme Court developed this test to guard against impermissible hindsight reconstruction in making obviousness determinations, for "[t]o imbue one of ordinary skill in the art with knowledge of the invention ... when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." *W.L. Gore & Associates v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983). "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1742 (2007). As such, "[h]indsight is not a justifiable basis on which to find that ultimate achievement of **a long sought and difficult scientific goal** was obvious." *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1209 (Fed. Cir. 1992) (emphasis added).

The claimed method is clearly within the realm of the "unpredictable arts" which include biotechnology. Applicants respectfully submit that the Examiner is using hindsight reconstruction as an improper basis upon which to reject the claims. Indeed, many of the references cited by the Examiner explicitly teach away from Applicants' claimed method. The Examiner appears to be summarily dismissing these teachings and bootstrapping disparate references together in formulaic rejections that are scientifically and legally without merit. The Examiner has not established a *prima facie* case of obviousness as is required by law and supported by the instant facts.

One of the advantages of the presently claimed method over the prior art is the fact that the MHC trimolecular complexes utilized in the claimed methods of detecting anti-MHC antibodies are **recombinantly truncated**: as such, they are no longer membrane bound but rather are **soluble** and thus **secreted** from the cell. The individual, soluble MHC trimolecular complexes can thereafter be easily purified away from other proteins while retaining their activity (i.e., conformation) and without denaturing the complexes.

US 5,482,841 is the only reference provided by the Examiner that is directed to methods for detecting anti-MHC antibodies; the '841 patent discloses an assay to determine the presence of

antibodies or other receptors specific for alloantigens. However, the '841 patent, as well as the secondary reference of DiBrino (i.e., the Examiner's own publication), utilize detergent solubilization methods for producing MHC molecules. MHC/HLA complexes produced by the detergent solubilization purification methods of these references will always include a **mixture** of HLA molecules; these references do not provide a method that utilizes purified **individual**, soluble MHC trimolecular complexes (wherein each complex contains the ***same*** class I MHC heavy chain molecule) as recited by the present claims. This fact alone negates a finding of obviousness over the cited references, as the '841 patent provides no mechanism for distinguishing between multiple alloantigens (i.e., multiple MHC/HLA molecules) obtained from a cellular source, and DiBrino used a cell line to produce HLA-B*4403 that also expresses HLA-Cw4 as well as HLA-B35 (see Zemmour et al.). The methods discussed in DiBrino (i.e., W6/32 immunoaffinity chromatography) are incapable of distinguishing between the three different HLA molecules produced. Therefore, the methods of DiBrino cannot logically and/or scientifically disclose or suggest a method of detecting anti-class I MHC antibodies directed to class I MHC complexes that contain a ***single*** class I MHC heavy chain, as the method taught by the combination of the '841 patent and DiBrino would utilize a mixture of MHC heavy chain molecules. Further, the methods of detergent solubilization described in the '841 patent and DiBrino result in lysis or **killing of the cells** in order to obtain the MHC molecule. In contrast, the subject claims explicitly recite that the host cells producing secreted MHC complexes **remain alive and therefore continue to produce class I MHC complexes**.

As the Examiner is surely aware, the prior art is good for everything it teaches, not just the invention it describes or claims. *EWP Corp. v. Reliance Universal, Inc.*, 755 F.2d 898 (Fed. Cir. 1985) ("on the issue of obviousness, the combined teachings of the prior art as a whole must be considered.") Furthermore, it is impermissible within the framework of Section 103 to pick and choose from any reference only so much of it as will support a given position, as the Examiner has done. Rather, everything in the reference must be considered in order to fully appreciate what the reference fairly suggests to one of ordinary skill in the art. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443 (Fed. Cir. 1990). As such, the entirety of the teachings of the '841 patent and the DiBrino reference may not be ignored or "excluded" from the other parts of said references, especially when such "excluded information" explicitly teaches away from a specifically claimed element.[1]

Therefore, Applicants respectfully submit that when the teachings of the '841 patent and the DiBrino reference are considered as a whole (as is required by law), a person having ordinary skill in the art would only find reason or suggestion to: (1) assay for the presence of antibodies directed to MHC class I trimolecular complexes that contain **multiple** different MHC class I heavy chains, with no mechanism of distinguishing between the different MHC class I heavy chains; and (2) utilize, in the assay of (1), MHC class I molecules that were produced utilizing detergent solubilization (i.e., lysing or killing) of cells (which contain multiple MHC/HLA molecules). Therefore, these two prior art references teach away from Applicants' recited claim steps of: (a) detecting the presence of anti-class I MHC antibodies in a sample utilizing soluble class I MHC trimolecular complexes wherein each complex comprises the same truncated, individual class I MHC heavy chain molecule; (a) obtaining the class I MHC trimolecular complexes utilized in (a) by "purifying individual soluble class I MHC trimolecular complexes substantially away from other proteins, wherein each trimolecular complex comprises identical soluble class I MHC heavy chain"; and (b) in the steps of obtaining the class I MHC trimolecular complexes utilized in (a), "harvesting the soluble class I MHC trimolecular complexes from the culture while

[1] See, e.g., "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be led in a direction divergent from the path that was taken by the applicant." *In re Haruna*, 249 F.3d 1327 (Fed. Cir. 2001); "A reference will teach away when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of the applicant's invention." *Syntex (USA) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005).

retaining the mammalian cell line in culture for production of additional soluble class I MHC trimolecular complexes". Thus, the '841 patent and the DiBrino references explicitly teach away from the presently claimed inventive concept(s).

The Examiner has recognized the deficiencies regarding the MHC complexes used in the anti-HLA assays of the '841 patent and has attempted to supply same with the teachings of DiBrino, McCluskey, Prilliman, Hausmann and Chen. As discussed herein above and as well as herein below, the DiBrino reference does nothing to remedy these deficiencies. While it is agreed that McCluskey discloses the desirability of purified, soluble class I MHC molecules, McCluskey teaches the formation of a hybrid molecule that fuses a **native** MHC class I molecule to a secreted immunoglobulin (Ig) molecule in order to produce a soluble chimeric protein. McCluskey teaches, therefore, the fusion of a secreted protein to a native MHC molecule, and **does not teach the mutagenesis of an HLA molecule so that it is secreted in its native form with no TM region**, as required by the presently claimed invention.

Prilliman is Applicants' earlier publication related to preliminary work performed by the Applicants prior to the presently disclosed and claimed inventive concept(s) being discovered. However, this preliminary work was performed to **isolate the peptides** presented in class I MHC heavy chain molecules, and does not provide a method of **purifying INTACT soluble individual class I MHC trimolecular complexes substantially away from other proteins for use in anti-MHC assays**. Declarations of the two instant co-inventors were filed in the subject application on January 22, 2009, and are incorporated herein by reference. Such declarations demonstrate in exhaustive detail that the methodology disclosed in Prilliman does not provide functionally active, individual soluble MHC trimolecular complexes that are purified substantially away from other proteins. Rather, Prilliman's methodology provides **denatured complexes** from which peptides can be obtained. In addition, Exhibit B of the Buchli declaration contains experimental data that clearly supports this fact and rebuts any arguments to the contrary set forth by the Examiner. Therefore, Prilliman does not teach a functionally active, individual soluble MHC trimolecular complex that is purified substantially away from other proteins such that the individual soluble MHC trimolecular complex maintains the physical, functional and antigenic integrity of the native MHC trimolecular complex.

In addition, the DiBrino reference is also directed to a method that involves isolation of peptides presented by class I MHC, and also utilizes an acidic elution step that denatures the trimolecular complexes in the same manner as described in Prilliman. The DiBrino reference and the '445 patent are directed to detergent solubilization methods, and thus teach away from the class I MHC complexes utilized in the presently claimed inventive concept(s).

The Hausmann and Chen references are also directed to detergent solubilization methods, and thus teach away from the presently claimed methods for the same reasons as presented herein above for the '841 patent and the DiBrino reference.

Therefore, and at most, the combination of references cited by the Examiner disclose that (1) it is desirable to conduct anti-HLA assays; (2) it is desirable to utilize purified, soluble class I MHC molecules in said anti-HLA assays; and (3) such production could involve detergent solubilization of cells, fusion of the MHC to a secreted Ig molecule to produce a chimeric molecule, or fusion of two or three of the components of the trimolecular complex to produce a single-chain MHC complex. The Federal Circuit has instructed that "[i]n order for a patent to be held invalid for obviousness, every claim limitation of the invention at issue must be found to exist in the prior art references" (see, *Velander v. Garner*, 348 F.3d 1359, 1363 (Fed. Cir. 2003). In addition, citing *In re Kahn* (449 (441 F.3d 977, 988 (Fed. Cir. 2006)), the Supreme Court in *KSR* sternly reminded the patent bar that "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." (emphasis added) The Examiner's instant analysis is, therefore, deficient and unsupportable by law and the scientific facts from each reference taken as a whole.

Thus, Applicants respectfully submit that the combination of US 5,482,841 in view of McCluskey, Prilliman, DiBrino, Hausmann and Chen does not teach all of the claimed limitations, and therefore a *prima facie* case of obviousness has not been established. Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. 103(a) rejection of claims 31-37, 45, 46, 49-51, 60 and 61 over this combination of references.

In response to the 35 U.S.C. 103(a) rejection of dependent claim 48 over the combination of references discussed herein above and further in view of Nakajima, Applicants respectfully submit that dependent claim 48 is non-obvious over the combination of US 5,482,841 and the McCluskey, Prilliman, DiBrino, Hausmann and Chen references for the reasons provided herein above in response to the rejection of claim 31 from which claim 48 depends. Further, Applicants respectfully submit that the Nakajima reference does nothing to remedy the deficiencies of these six references, and thus the combination of seven references do not teach each and every claim limitation of claim 48. Therefore, a *prima facie* case of obviousness has not been established. Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. 103(a) rejection of claim 48 over this combination of seven references.

In summary, Applicants respectfully submit that claims 31-38, 45-46, 48-51, and 60-61 are patentable over the art of record and in a condition for allowance. Applicants respectfully request reconsideration and withdrawal of the two 35 U.S.C. 103(a) rejections of the claims, and passage of the subject application to allowance. Further, upon allowance of any of the generic claims, Applicants respectfully request rejoinder and reconsideration of currently withdrawn claims 38-40, as well as all other non-elected species.

Respectfully submitted,

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